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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,706	10/17/2003	Kay O. Broschat	01393/1	1944

7590 11/26/2004

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EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/688,706	BROSCHAT ET AL.
	Examiner	Art Unit
	Jon B. Ashen	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) 1-18,21-27 and 29-32 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 19,20 and 28 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-18, drawn to an antisense compound targeted to a nucleic acid molecule encoding GFAT, classified in class 536, subclass 24.5.

   II. Claims 19-32, drawn to a method of treatment comprising inhibiting the expression of mPGES-1 in cells, tissues or a human, classified in class 514, subclass 44.

2. Claims 4-7 are subject to an additional restriction since the sequences listed as SEQ ID Nos: 1-3063 are not considered to be a proper genus/Markush. See MPEP 803.02 - PRACTICE RE MARKUSH-TYPE CLAIMS - If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention

exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Claims 4-7 specifically claim antisense sequences as listed, which are targeted to and modulate the expression of GFAT. Although the antisense sequences claimed each target and modulate expression of GFAT, the instant antisense sequences are considered to be unrelated, since each antisense sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of a GFAT nucleic acid, and absent evidence to the contrary, each antisense, upon binding to a GFAT nucleic acid, is expected to functionally modulate (increase or decrease) the expression of GFAT to varying degrees. As such the Markush/genus of antisense sequences in claims 4-7 are not considered to constitute a proper genus, and are therefore subject to restriction.

Furthermore, a search of more than one (1) of the antisense sequences claimed in claims 4-7 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences. MPEP 808.02 states in part: Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05(C) - 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must shown by appropriate explanation one of the following:

(C) A different field of search: Where it is necessary to search for one of the distinct subjects in places where no pertinent art to the other subject exists, a different field of search is shown, even though the two are classified together.

It is noted that a search of the available sequence databases produces a listing of references disclosing the sequence most similar to the query sequence. This is the "place" where the examiner searches for prior art. The prior art relating to another query sequence will not be found in this "place"- a different listing of references must be generated and searched by the examiner. Thus a different search is shown, and restriction is proper.

In view of the foregoing, one (1) antisense sequence is considered to be a reasonable number of sequences for examination. Accordingly, applicant is required to elect one (1) sequence from claims 4-7 that will be examined on the merits. Note that this is not a species election.

The inventions are distinct, each from the other because of the following reasons:

3. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). Invention I is drawn to an antisense compound targeted to a nucleic acid molecule encoding GFAT. Invention II is drawn to a method of treatment comprising inhibiting the expression of mPGES1 in cells, tissues or a

human. In the instant case the product as claimed can be used in a materially different process of using that product such as a hybridization probe to elucidate cell or tissue specific gene expression of GFAT.

Furthermore, searching inventions I and II together would impose a serious search burden. In the instant case, prior art searches of an compound sequence and a method of using said compound sequence are not coextensive. Search of each of these inventions would require different key word and sequence searches in different patent, non-patent literature and sequence databases and require, at least, specific searches for particular method steps of invention II not required for the search of invention I. These searches would then require subsequent in-depth analysis of all relevant prior art literature and sequence references, placing a serious burden on the Office in terms of both search and examination. As such, it would be burdensome to perform examination of inventions I and II together.

4. Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification and would require divergent searches of sequence and literature databases placing an undue administrative burden on the examiner, restriction for examination purposes as indicated is proper.

5. This application contains claims directed to the following patentably distinct species of the claimed invention: The diseases or conditions listed in claims 21-32 that are to be treated by the method of claim 20.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 20 is generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Status of the Application

6. During a telephone conversation with Christopher Bauer on 10/15/04 a provisional election was made with traverse to prosecute the invention of Group II, claims 19-32 and the species of disease/condition that is diabetes as set forth in claim 28. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-18, 21-27 and 29-32 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. It is noted herein that claims 19 and 20, which depend on withdrawn claim 2, are considered indefinite (see 112 2nd paragraph rejection below). However, in the interests of compact prosecution and because Applicant's phone election precluded amendment of the improper claim dependency, the limitations of claim 2 will be imparted into claims 19, 20 and 28 (which depends from claim 20) only insofar as the subject matter of claim 2 reads on the elected invention.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The instant application claims benefit of priority to an earlier filed application (U.S Provisional Application 60,419,268). However, support for claims 19, 20 and 28 (which depends from claim 20), drawn to methods of inhibiting mPGES-1, could not be found in the earlier filed document. If Applicant believes that such support is present in said document, Applicant should point out, with particularity, where such support is to be found.

Specification

8. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 19 and 20 (and claim 28 which depends from claim 20) are drawn to a method of treatment comprising inhibiting the expression of mPGES-1 in cells or tissues or a human using an antisense compound targeted to a nucleic acid molecule encoding a human GFAT. However, the meaning of the term "mPGES-1" is not apparent from the descriptive portion of the specification which does not provide any description of what "mPGES-1" is or refers to, or provide a clear disclosure as to its import.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 19 and 20 (and claim 28 which depends from claim 20) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 19 and 20 recite the limitation "the antisense compound of claim 2". There is insufficient antecedent basis for this limitation in these claims because claim 2 has been withdrawn in the instant application. Additionally, claims 19 and 20 are both drawn to methods of inhibiting the expression of "mPGES-1." However, one of skill in the art cannot determine the metes and bounds of claims drawn to methods of inhibiting

the expression of mPGES-1 because the nature or identity of mPGES-1 cannot be determined (without making assumptions as to what is represented by the abbreviation "mPGES-1) from the disclosures of either the specification or the claims as filed. What is mPGES-1?

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 19, 20 and 28 (which depends from claim 20) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 19 and 20 (and claim 28 which depends from claim 20) are drawn to a method of treatment as outlined previously in this action. The instant claims are drawn to a method of treatment wherein an antisense compound targeted to the nucleotide sequence encoding GFAT is used to inhibit the expression of mPGES-1.

The specification as filed, however, does not disclose or describe anything in regards to mPGES-1, providing no specific or general guidance as to what is encompassed by the method of treatment as claimed. Therefore, the claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2nd 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed (see page 1117). Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Therefore, because there is no disclosure of any kind concerning mPGES-1 in the specification as filed, there is no indication that applicant was in possession of a method of treatment comprising inhibiting mPGES-1 using an antisense compound targeted to GFAT.

13. Claims 19, 20 and 28 (which depends from claim 20) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claims 19, 20 and 28 is outlined above. All claims are drawn to a method of treatment comprising inhibiting the expression of mPGES-1 using an antisense compound targeted to GFAT. In the instant case, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the method as claimed.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The scope of claims 19, 20 and 28 is broadly drawn to a method of treatment comprising inhibiting the *in vivo* expression of mPGES-1 in any cells or tissues of any organism (including humans). The specification as filed, however, provides no support for claims to a therapeutic method of inhibiting mPGES-1 using an antisense compound targeted to GFAT or, in fact, any other antisense compound because the specification provides no disclosure of any kind concerning the indentity or nature of mPGES-1. It is respectfully pointed out here that it is unclear how the skilled artisan would practice the method of inhibiting the expression of mPGES-1 using an antisense compound targeted

to GFAT when the identity or nature of mPGES-1 is unknown and cannot be determined (as set forth above in the rejection under 112 2nd paragraph).

The methods recited in these claims indicate that the nature of this invention is a technique for antisense inhibition of gene expression *in vivo*, specifically an *in vivo* therapeutic method of antisense inhibition of mPGES-1 gene expression in cells, tissues or organisms using an antisense compound targeted to GFAT. The specification provides no disclosure of the identity of mPGES-1, no disclosure of methods of inhibiting the expression of mPGES-1, no examples of antisense inhibition of mPGES-1 gene expression using antisense compounds targeted to GFAT and no specific or general guidance that would allow the skilled artisan to practice the method as claimed. The specification as filed fails to even mention mPGES-1.

The state of the art at the time of filing, relative to the enablement of the antisense therapies *in vivo,* recognizes that there is a high degree of unpredictability in the art due to obstacles that continue, to the present day, to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) including for example, problems with delivery and target accessibility. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic antisense method.

Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514) provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating

human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511).

In regards to the delivery of therapeutic nucleic acids, Jen et al. (Stem Cells 2000, Vol. 18, p 307-319) state (pg. 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (pg. 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Crooke, 2004 (Annu. Rev. Med. Vol. 55, pp. 61-95) discusses the particular problems associated with target accessibility wherein he states (in post filing art), "Selection of sites for induction of optimal antisense activity in an RNA molecule is dependent on the terminating mechanism and influenced by the chemical class of the

compound. Each RNA appears to display unique patterns of sites of sensitivity. Within the phosphorothiopate oligodeoxynucleotide chemical class, antisense activity can vary from undetectable to 100% by shifting an compound by just a few bases in the RNA target (references omitted). Despite significant progress in developing general rules that help define potentially optimal sites in RNA species, to a large extent, this remains an empirical process that must be performed for each RNA target and every new chemical class of compounds" (pg. 71, 4th paragraph).

Given this unpredictability, in particular in regards to targeting and delivery of antisense compounds, the skilled artisan would require specific guidance to practice the claimed method *in vivo*, with a resultant therapeutic outcome, as claimed. The instant specification does not show how one in the art might overcome the obstacles to providing antisense therapy as outlined above or how applicant has overcome the same general obstacles to antisense therapy in the instant invention.

Additionally, because no specific or functional species of antisense compounds that would be necessary to practice the method of treatment as claimed are disclosed in the specification, the skilled artisan would have to perform an extremely large and undue quantity of trial and error experimentation (as indicated above) in order to determine *de novo* the structure and function of an antisense compound that would function in the *in vivo* method of treatment as claimed. Based on the complete lack of guidance in the specification regarding the direction in which the experimentation should proceed, even if the *de novo* experiments required were considered routine by those of skill in the art, the more or less standard nature of each experiment would be

outweighed by the sheer quantity of undue trial and error experimentation required to determine how to practice the method of the instant invention.

In conclusion, due to the nature of the invention as an *in vivo* method of treatment, the degree of unpredictability in the art of antisense therapy, the breadth of the claimed method as an *in vivo* method of treatment for diabetes in any cells, tissues or organism, the lack of guidance as to what particular species of antisense nucleic acids would be required to practice the method as claimed, the need to screen multiple species of said nucleic acids so as to allow identification of particular species as functional within the method of treatment as claimed and the quantity of *de novo* experimentation necessary to discover the above, an undue amount of experimentation would be required in order to practice the method of treatment as claimed. Therefore, the inventors have not enabled one skilled in the art perform the method of the claimed invention.

Claim Rejections - 35 USC § 101

14. Claims 19, 20 and 28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 19 and 20 (and claim 28 which depends from claim 20) are drawn to a method of treatment as outlined previously in this action. However, the instant specification does not disclose or provide any suggestion or indication as to what is being claimed by a method of inhibiting "mPGES-1" because the specification does

not disclose or provide any suggestion or indication as to what "mPGES-1" is. Therefore, claims drawn to a method of inhibiting "mPGES-1" are not supported by a specific and substantial asserted utility (because none has been set forth in the instant specification) or a well established utility (because the nature or identity of "mPGES-1" cannot be determined).

Claims 19, 20 and 28 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specifc and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

15. No claim currently under examination is in condition for allowance. Claims 19, 20 and 28 were free of the prior art searched.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba